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L5 ANSWER 1 OF 9 CAPLUS COPYRIGHT 2003 ACS on STN
2003:526961 Document No. 139:132192 A new monoclonal antibody, mAb 204-II, that influences the binding of platelet GPVI to fibrous collagen. Moroi, Masaaki; Mizuguchi, Jun; Kawashima, Sachiko; Nagamatsu, Michiko; Miura, Yoshiki; Nakagaki, Tomohiro; Ito, Katsuaki; Jung, Stephanie M. (Department of Protein Biochemistry, Institute of Life Science, Kurume University, Fukuoka, Japan). Thrombosis and Haemostasis, 89(6), 996-1003 (English) 2003. CODEN: THHADQ. ISSN: 0340-6245. Publisher: Schattauer GmbH.
AB The newly identified platelet collagen receptor glycoprotein VI binds to fibrous collagen, inducing platelet activation. Several antibodies against GPVI have been reported, including a patient's auto-antibodies, that activates platelets through their ability to crosslink this glycoprotein. The authors have developed a monoclonal antibody (mAb) against GPVI using the recombinant extracellular domain of GPVI as an antigen. This antibody, mAb 204-II, induced platelet aggregation and tyrosine phosphorylation of proteins similar to those induced by GPVI-reactive proteins, collagen and convulxin. Its interaction with GPVI was analyzed by measuring the effect of the antibody on GPVI binding to collagen using a dimeric form of recombinant GPVI, GPVI-Fc2. MAb 204-II inhibited the binding of GPVI-Fc2 to fibrous collagen particles, but enhanced the GPVI binding to immobilized collagen, suggesting that the antibody binds to a region near the collagen binding site of GPVI. MAb 204-II also inhibited the GPVI binding to convulxin at a low concn., but not completely. Since mAb 204-II reacts specifically with GPVI and is applicable for immunoblotting and immunopptn., this antibody would be useful for studies on GPVI.

L5 ANSWER 2 OF 9 EMBASE COPYRIGHT 2003 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
2003422560 EMBASE Stejnulxin, a novel snake C-type lectin-like protein from Trimeresurus stejnegeri venom is a potent platelet agonist acting specifically via GPVI. Lee W.-H.; Du X.-Y.; Lu Q.-M.; Clemetson K.J.; Zhang Y.. Dr. Y. Zhang, Department of Animal Toxinology, Kunming Institute of Zoology, Chinese Academy of Sciences, 32 East Jiao Chang Road, Kunming,

Yunnan 650223, China. zhangy@mail.kiz.ac.cn. Thrombosis and Haemostasis 90/4 (662-671) 1 Oct 2003.
Refs: 34.
ISSN: 0340-6245. CODEN: THHADQ. Pub. Country: Germany. Language: English. Summary Language: English.

AB Stejnulxin, a novel snake C-type lectin-like protein with potent platelet activating activity, was purified and characterized from Trimeresurus stejnegeri venom. Under non-reducing conditions, it migrated on a SDS-polyacrylamide gel with an apparent molecular mass of 120 kDa. On reduction, it separated into three polypeptide subunits with apparent molecular masses of 16 kDa (.alpha.), 20 kDa (.beta.(1)) and 22 kDa (.beta.(2)), respectively. The complete amino acid sequences of its subunits were deduced from cloned cDNAs. The N-terminal sequencing and cDNA cloning indicated that .beta.(1) and .beta.(2) subunits of stejnulxin have identical amino acid sequences and each contains two N-glycosylation sites. Accordingly, the molecular mass difference between .beta.(1) and .beta.(2) is caused by glycosylation heterogenity. The subunit amino acid sequences of stejnulxin are similar to those of convulxin, with sequence identities of 52.6% and 66.4% for the .alpha. and .beta., respectively. Stejnulxin induced human platelet aggregation in a dose-dependent manner. Antibodies against .alpha.(IIIb).beta.(3) inhibited the aggregation response to stejnulxin, indicating that activation of .alpha.(IIIb).beta.(3) and binding of fibrinogen are involved in stejnulxin-induced platelet aggregation. Antibodies against GPIb.alpha. or .alpha.(2).beta.(1) as well as echicetin or rhodocetin had no significant effect on stejnulxin-induced platelet aggregation. However, platelet activation induced-by stejnulxin was blocked by anti-GPVI antibodies. In addition, stejnulxin induced a tyrosine phosphorylation profile in platelets that resembled that produced by convulxin. Biotinylated stejnulxin bound specifically to platelet membrane GPVI.

L5 ANSWER 3 OF 9 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
2002:407412 Document No.: PREV200200407412. Involvement of glycoprotein VI in platelet thrombus formation on both collagen and von Willebrand factor surfaces under flow conditions. Goto, Shinya; Tamura, Noriko; Handa, Shunnosuke; Arai, Morio; Kodama, Kumi; Takayama, Hiroshi [Reprint author]. Department of Hematology and Oncology, Clinical Sciences for Pathological Organs, Graduate School of Medicine, Kyoto University, 54 Shogoin-Kawaracho, Sakyo-ku, Kyoto, 606-8507, Japan. shinichi@is.icc.u-tokai.ac.jp; hiro@kuhp.kyoto-u.ac.jp. Circulation, (July 9, 2002) Vol. 106, No. 2, pp. 266-272. print.
CODEN: CIRCAZ. ISSN: 0009-7322. Language: English.

AB Background: We studied the role of glycoprotein (GP) VI in platelet adhesion and thrombus formation on the immobilized collagen and von Willebrand factor (vWF) surface under flow conditions. Methods and Results: Whole blood obtained from 2 patients with GP VI-deficient platelets and the effects of the Fab of anti-GP VI antibody (Fab/anti-GP VI) were tested. Blood containing platelets rendered fluorescent by mepacrine was perfused on immobilized type I collagen or vWF under controlled wall shear rate. Platelet adhesion and thrombus formation were detected by epifluorescent videomicroscopy. The percentage of surface coverage by the platelets was calculated. Fc receptor gamma-chain and spleen tyrosine kinase (Syk) were immunoprecipitated from the lysate of platelets stimulated by vWF plus ristocetin and then analyzed by antiphosphotyrosine immunoblotting. No platelet attachment was seen on the surface of collagen even after 9 minutes of perfusion of blood at relatively low (100 s-1) or high (1500 s-1) wall shear rate, either in the case of blood containing GP VI-deficient platelets or in the presence of Fab/anti-GP VI, whereas significant platelet thrombus formation was noted after control blood perfusion. Such interference with the actions of GP VI also reduced firm platelet adhesion on immobilized vWF. vWF-induced tyrosine phosphorylation of GP VI-associated Fc receptor gamma-chain followed by Syk activation occurred in normal platelets, but little activation of Syk occurred in GP VI-deficient platelets. Conclusions: GP VI plays crucial roles in platelet thrombus formation on the surface of

collagen under flow conditions in humans and is also involved in the process of firm platelet adhesion on the surface of vWF.

L5 ANSWER 4 OF 9 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
2003:60975 Document No.: PREV200300060975. Anti GPVI human antibodies neutralizing collagen-induced platelet aggregation isolated from a combinatorial phage display library. Qian, Ming D.; Villeval, Jean-Luc; Xiong, Ximing; Jandrot-Perrus, Martine; Nagashima, Kumiko; Tonra, James; McDonald, Kevin; Goodearl, Andrew; Gill, Davinder [Reprint Author]. Millennium Pharmaceuticals, Inc., 640 Memorial Drive, Cambridge, MA, 02139, USA. gill@mpi.com. Human Antibodies, (2002) Vol. 11, No. 3, pp. 97-105. print.
ISSN: 1093-2607. Language: English.

AB Glycoprotein VI is a type I membrane protein identified as a key platelet receptor for collagen. In vitro binding of the GPVI receptor with collagen leads to activation and ultimately to aggregation of platelets. In vivo, GPVI-collagen interactions could cause formation of occlusive thrombi within vessels with damaged endothelial barriers. GPVI antagonists are therefore important therapeutics in patients suffering from collagen-mediated ischemic disorders such as myocardial infarction or stroke. Polyclonal antibodies to GPVI prepared from one patient serum have previously been described. However, only their monovalent Fab fragments, incapable of receptor crosslinking, were found to protect platelets from collagen-mediated aggregation. Here we describe GPVI-neutralizing human antibodies derived from a combinatorial phage display library of single-chain antibodies. By selecting phage on GPVI-expressing U937 cells, we isolated five specific antibodies - A4, A9, A10, C3 and C9. Of the set A10 and C3 specifically blocked GPVI binding to collagen-rich adventitial layers in aorta sections. The higher affinity antibody A10 inhibited binding of snake-venom convulxin to GPVI. It also specifically protected human platelets from collagen-induced aggregation in vitro. A10-bound platelets could still be activated by ADP or thrombin suggesting that this human scFv may represent an original anti-platelet agent for the treatment of collagen-mediated thrombotic diseases.

L5 ANSWER 5 OF 9 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
2003:336538 Document No.: PREV200300336538. Identification of the Collagen Binding Surface of Human Glycoprotein VI and Functional Blockade by a Novel Human Recombinant Antibody. Smethurst, Peter A. [Reprint Author]; Joutsi-Korhonen, Lotta [Reprint Author]; Connor, Marie N. O [Reprint Author]; Jennings-Foad, Nicola S. [Reprint Author]; Wilson, Erica [Reprint Author]; Garner, Stephen F. [Reprint Author]; Zhang, Yanjun [Reprint Author]; Knight, Graham [Reprint Author]; Onley, David J. [Reprint Author]; Harmer, Ian J. [Reprint Author]; Dafforn, Timothy R. [Reprint Author]; IJsseldijk, Martin [Reprint Author]; de Groot, Philip G. [Reprint Author]; Watkins, Nicholas A. [Reprint Author]; Farndale, Richard W. [Reprint Author]; Ouwehand, Willem H. [Reprint Author]. Department of Haematology, University of Cambridge and National Blood Service, Cambridge, UK. Blood, (November 16, 2002) Vol. 100, No. 11, pp. Abstract No. 1840. print.
Meeting Info.: 44th Annual Meeting of the American Society of Hematology. Philadelphia, PA, USA. December 06-10, 2002. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971. Language: English.

AB Glycoprotein (GP) VI is the major receptor responsible for activation of platelets by collagen. Our aim is to define the collagen binding site of GPVI to inform the development of a blocking antibody which may be considered useful as an anti-thrombotic drug. We recombinantly expressed the tandem Ig like folds of human GPVI (hD1D2) and various mutant forms as fusion proteins with a calmodulin affinity tag. In this form they showed specific binding to collagen-related peptide (CRP) in a plate assay. Certain mutations reduced the strength of this binding. By structural modelling, these are predicted to occupy the apical surface of hD1D2, suggesting that the collagen binding surface on GPVI is analogous to that

of the killer cell inhibitory receptors (KIRs). hD1D2 was also used as bait to select single chain variable domain antibody fragments (scFvs) from human V gene phage display libraries. ScFvs specific for hGPVI were obtained, with various functional properties. An inhibitor, scFv 10B12, which was originally selected by its ability (as a phage antibody) to disrupt the hD1D2:CRP interaction, effectively inhibits the interaction of platelet GPVI with collagen. A second, scFv 1C3, selected by its ability simply to bind hD1D2 in solution, did not inhibit and serves as a control. V gene sequencing allowed certain structural characteristics of these antibodies to be identfied. A combination of receptor mutagenesis and structural modelling have revealed the epitope for 10B12 on domain 1, providing convergent evidence for the location of the collagen binding surface and a basis for the rational improvement of scFv 10B12 as a designer GPVI antagonist of therapeutic potential.

L5 ANSWER 6 OF 9 CAPLUS COPYRIGHT 2003 ACS on STN

2001:12605 Document No. 134:81775 Glycoprotein VI cDNA and protein from human and murine blood platelets and their diagnostic and therapeutic applications. Busfield, Samantha J.; Villelal, Jean-luc; Jandrot-Perrus, Martine; Vainchencker, William; Gill, Davinder Singh; Qian, Ming Diana; Kingsbury, Gillian (Millennium Pharmaceuticals, Inc., USA). PCT Int. Appl. WO 2001000810 A1 20010104, 227 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US18152 20000630. PRIORITY: US 1999-345468 19990630; US 1999-454824 19991206; US 2000-503387 20000214.

AB The invention provides isolated cDNA mols. and polypeptide mols. that encode human and murine glycoprotein VI, a platelet membrane glycoprotein that is involved platelet-collagen interactions. The protein initially designated TANGO 268 represents the platelet-expressed collagen receptor glycoprotein VI (GPVI) based on the following evidence: (1) the glycosylated mol. wts. of TANGO 268 and GPVI are identical or similar; (2) both are recognized by anti-GPVI antibodies and bind to convulxin; (3) both are preferentially expressed in megakaryocytic cells; (4) both ar predicted to have a single N-glycosylation site; (5) the mol. mass of GPVI upon N- and O-linked glycosylation is .apprx.62 kDa, that of GPVI; (6) two Ig-like domains in TANGO 268 indicates interaction with FcR.gamma.; (7) the absence of a large intracytoplasmic tail suggests that this membrane-bound glycoprotein has no signaling role but assocs. with another member of the Ig family; and (8) TANGO 268 has a charged arginine residue in the transmembrane domain which is also predicted to be present in GPVI. The human gene for GPVI was mapped on radiation hybrid panels to the long arm of chromosome 19, in the region 19q13, syntenic to mouse chromosome 7. The invention also provides antisense nucleic acid mols., expression vectors contg. the nucleic acid mols. of the invention, host cells into which the expression vectors have been introduced, and non-human transgenic animals in which a nucleic acid mol. of the invention has been introduced or disrupted. The invention still further provides isolated polypeptides, fusion polypeptides, antigenic peptides and antibodies. Diagnostic, screening and therapeutic methods utilizing compns. of the invention are also provided.

L5 ANSWER 7 OF 9 EMBASE COPYRIGHT 2003 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

2001406289 EMBASE Bilinexin, a snake C-type lectin from Agkistrodon bilineatus venom agglutinates platelets via GPIb and .alpha.(2).beta.(1). Du X.-Y.; Navdaev A.; Clemetson J.M.; Magnenat E.; Wells T.N.C.; Clemetson K.J.. Dr. K.J. Clemetson, Theodor Kocher Institute, University of Berne, Freie Strasse 1, CH-3012 Berne, Switzerland. clemetson@tki.unibe.ch. Thrombosis and Haemostasis 86/5 (1277-1283) 2001.

Refs: 25.
ISSN: 0340-6245. CODEN: THHADQ. Pub. Country: Germany. Language: English. Summary Language: English.

AB A new snake protein, named bilinexin, has been purified from Agkistrodon bilineatus venom by ion-exchange chromatography and gel filtration chromatography. Under non-reducing conditions it has a mass of 110 kDa protein on SDS-PAGE. On reduction, it can be separated into five subunits with masses in the range 13-25 kDa. The N-terminal sequences of these subunits are very similar to those of convulxin or the alboaggregins, identifying bilinexin as a new member of the snake C-type lectin family, unusual in having multiple subunits. Bilinexin agglutinates fixed platelets, washed platelets and platelet rich plasma (PRP) without obvious activation (shape change) as confirmed by light microscope examination. Both inhibitory and binding studies indicate that antibodies against .alpha.(2).beta.(1) inhibit not only platelet agglutination induced by bilinexin, but also bilinexin binding to platelets. VM16d, a monoclonal anti-GPIb.alpha. antibody, completely inhibits platelet agglutination induced by bilinexin, and polyclonal antibodies against GPIb.alpha. prevent its binding to platelets. However, neither convulxin, polyclonal anti-GPVI antibodies, nor GPIIb/IIIa inhibitors affect its binding to and agglutination of platelets. Bilinexin neither activates GPIIb/IIIa integrin on platelets nor induces tyrosine phosphorylation of platelet proteins, nor increases intracellular Ca(2+) in platelets. Like alboaggregin B, bilinexin agglutinates platelets, which makes it a good tool to investigate the differences in mechanism between snake C-type lectins causing platelet agglutination and those that induce full activation.

L5 ANSWER 8 OF 9 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
2000:417229 Document No.: PREV200000417229. Expression and function of the mouse collagen receptor glycoprotein VI is strictly dependent on its association with the FcRgamma chain. Nieswandt, Bernhard [Reprint author]; Bergmeier, Wolfgang; Schulte, Valerie; Rackebrandt, Kirsten; Gessner, J. Engelbert; Zirngibl, Hubert. IMMI, Klinikum Wuppertal, Universitaet Witten-Herdecke, Heusnerstrasse 40, D-42283, Wuppertal, Germany. Journal of Biological Chemistry, (August 4, 2000) Vol. 275, No. 31, pp. 23998-24002. print.
CODEN: JBCHA3. ISSN: 0021-9258. Language: English.

AB Platelet glycoprotein (GP) VI has been proposed as the major collagen receptor for activation of human platelets. Human GPVI belongs to the immunoglobulin superfamily and is noncovalently associated with the FcRgamma chain that is involved in signaling through the receptor. In mice, similar mechanisms seem to exist as platelets from FcRgamma chain-deficient mice do not aggregate in response to collagen. However, the activating collagen receptor on mouse platelets has not been definitively identified. In the current study we examined the function and in vivo expression of GPVI in control and FcRgamma chain-deficient mice with the first monoclonal antibody against GPVI (JAQ1). On wild type platelets, JAQ1 inhibited platelet aggregation induced by collagen but not PMA or thrombin. Cross-linking of bound JAQ1, on the other hand, induced aggregation of wild type but not FcRgamma chain-deficient platelets. JAQ1 stained platelets and megakaryocytes from wild type but not FcRgamma chain-deficient mice. Furthermore, JAQ1 recognized GPVI (approximately 60 kDa) in immunoprecipitation and Western blot experiments with wild type but not FcRgamma chain-deficient platelets. These results strongly suggest that GPVI is the collagen receptor responsible for platelet activation in mice and demonstrate that the association with the FcRgamma chain is critical for its expression and function.

L5 ANSWER 9 OF 9 MEDLINE on STN DUPLICATE 1
1999273390 Document Number: 99273390. PubMed ID: 10341844.
Collagen-platelet interaction: Gly-Pro-Hyp is uniquely specific for platelet Gp VI and mediates platelet activation by collagen. Knight C G; Morton L F; Onley D J; Peachey A R; Ichinohe T; Okuma M; Farndale R W; Barnes M J. (Biochemistry Department, Cambridge University, UK.)

CARDIOVASCULAR RESEARCH, (1999 Feb) 41 (2) 450-7. Journal code: 0077427. ISSN: 0008-6363. Pub. country: Netherlands. Language: English.

AB OBJECTIVE: Peptides consisting of a repeat Gly-Pro-Hyp sequence are potent platelet agonists. The aim of this study was: (1) to examine the specificity of this sequence for platelet activation; (2) to confirm its recognition by platelet glycoprotein VI; and (3) to assess with suitable peptides the relative importance of glycoprotein VI and integrin alpha 2 beta 1 in platelet activation by collagen. METHODS: Peptides were synthesized by standard Fmoc chemistry and tested for their ability to support adhesion of human platelets and HT 1080 cells, induce platelet aggregation, bind integrin alpha 2 subunit A-domain and to cause tyrosine phosphorylation of platelet proteins. RESULTS: (1) Peptides consisting of a repeat Gly-Pro-Pro, Gly-Pro-Ala or Gly-Pro-Arg sequence exhibited little if any platelet-reactivity. (2) The platelet-reactive peptide consisting of a repeating Gly-Pro-Hyp sequence failed to induce tyrosine phosphorylation in glycoprotein VI-deficient platelets. Platelet adhesion to this peptide was inhibited by intact anti-**glycoprotein VI antibody** and its Fab fragment. The latter inhibited aggregation by the peptide and fibres of both collagens I and III. (3) A peptide containing a 15-mer alpha 2 beta 1-binding sequence in a repeat Gly-Pro-Pro structure supported alpha 2 beta 1-mediated platelet and HT 1080 cell adhesion and bound alpha 2 A-domain, but failed to activate platelets or to induce tyrosine phosphorylation. Conversely, a peptide containing this sequence but with an essential Glu replaced by Ala and inserted in a repeat Gly-Pro-Hyp structure did not recognize alpha 2 beta 1, but was highly platelet activatory. CONCLUSIONS: Platelet activation by collagen involves the highly-specific recognition of the Gly-Pro-Hyp sequence by platelet glycoprotein VI. Recognition of alpha 2 beta 1 is insufficient to cause activation. Interaction between collagen and glycoprotein VI is unique since Gly-Pro-Hyp is common in collagens but occurs rarely in other proteins, and glycoprotein VI may be expressed solely by platelets. This sequence could provide a basis for a highly-specific anti-thrombotic reagent to control thrombosis associated with plaque rupture.

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=> s glycoprotein VI
L6          775 GLYCOPROTEIN VI

=> s l6 and platelet collagen receptor
L7          163 L6 AND PLATELET COLLAGEN RECEPTOR

=> s l7 and antibod?
L8           46 L7 AND ANTIBOD?

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L9           15 DUP REMOVE L8 (31 DUPLICATES REMOVED)

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L9 ANSWER 1 OF 15 MEDLINE on STN DUPLICATE 1

2003257954 Document Number: 22667794. PubMed ID: 12783112. A new monoclonal **antibody**, mAb 204-11, that influences the binding of platelet GPVI to fibrous collagen. Moroi Masaaki; Mizuguchi Jun; Kawashima Sachiko; Nagamatsu Michiko; Miura Yoshiki; Nakagaki Tomohiro; Ito Katsuaki; Jung Stephanie M. (Department of Protein Biochemistry, Institute of Life Science, Kurume University, 2432-3 Aikawa-machi, Kurume, Fukuoka-ken, 839-0861, Japan.. mmoroi@mbox.lsi.kurume-u.ac.jp) . THROMBOSIS AND HAEMOSTASIS, (2003 Jun) 89 (6) 996-1003. Journal code: 7608063. ISSN: 0340-6245. Pub. country: Germany: Germany, Federal Republic of. Language: English.

AB The newly identified **platelet collagen receptor glycoprotein VI** binds to fibrous collagen, inducing platelet activation. Several **antibodies**

against GPVI have been reported, including a patient's auto-**antibodies**, that activates platelets through their ability to crosslink this glycoprotein. We have developed a monoclonal **antibody** (mAb) against GPVI using the recombinant extracellular domain of GPVI as an antigen. This **antibody**, mAb 204-11, induced platelet aggregation and tyrosine phosphorylation of proteins similar to those induced by GPVI-reactive proteins, collagen and convulxin. Its interaction with GPVI was analyzed by measuring the effect of the **antibody** on GPVI binding to collagen using a dimeric form of recombinant GPVI, GPVI-Fc2. MAb 204-11 inhibited the binding of GPVI-Fc2 to fibrous collagen particles, but enhanced the GPVI binding to immobilized collagen, suggesting that the **antibody** binds to a region near the collagen binding site of GPVI. MAb 204-11 also inhibited the GPVI binding to convulxin at a low concentration, but not completely. Since mAb 204-11 reacts specifically with GPVI and is applicable for immunoblotting and immunoprecipitation, this **antibody** would be useful for studies on GPVI.

L9 ANSWER 2 OF 15 MEDLINE on STN *DUPLICATE 2*

2003032268 Document Number: 22403964. PubMed ID: 12515812. A crucial role of **glycoprotein VI** for platelet recruitment to the injured arterial wall in vivo. Massberg Steffen; Gawaz Meinrad; Gruner Sabine; Schulte Valerie; Konrad Ildiko; Zohlnhofer Dietlind; Heinzmann Ulrich; Nieswandt Bernhard. (Deutsches Herzzentrum und 1. Medizinische Klinik, Technische Universitat Munchen, D-80636 Munchen, Germany.) JOURNAL OF EXPERIMENTAL MEDICINE, (2003 Jan 6) 197 (1) 41-9. Journal code: 2985109R. ISSN: 0022-1007. Pub. country: United States. Language: English.

AB Platelet adhesion and aggregation at sites of vascular injury is crucial for hemostasis but may lead to arterial occlusion in the setting of atherosclerosis and precipitate diseases such as myocardial infarction. A current hypothesis suggests that platelet glycoprotein (GP) Ib interaction with von Willebrand factor recruits flowing platelets to the injured vessel wall, where subendothelial fibrillar collagens support their firm adhesion and activation. However, so far this hypothesis has not been tested in vivo. Here, we demonstrate by intravital fluorescence microscopy of the mouse carotid artery that inhibition or absence of the major **platelet collagen receptor**, GPVI, abolishes platelet-vessel wall interactions after endothelial denudation. Unexpectedly, inhibition of GPVI by the monoclonal **antibody** JAQ1 reduced platelet tethering to the subendothelium by approximately 89%. In addition, stable arrest and aggregation of platelets was virtually abolished under these conditions. Using different models of arterial injury, the strict requirement for GPVI in these processes was confirmed in GPVI-deficient mice, where platelets also failed to adhere and aggregate on the damaged vessel wall. These findings reveal an unexpected role of GPVI in the initiation of platelet attachment at sites of vascular injury and unequivocally identify platelet-collagen interactions (via GPVI) as the major determinant of arterial thrombus formation.

L9 ANSWER 3 OF 15 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN

2002:295240 The Genuine Article (R) Number: 534WQ. Integrin alpha(2)-deficient mice develop normally, are fertile, but display partially defective platelet interaction with collagen. Holtkotter O; Nieswandt B; Smyth N; Muller M; Hafner M; Schulte V; Krieg T; Eckes B (Reprint). Univ Cologne, Dept Dermatol, Joseph Stelzmann Str 9, D-50931 Cologne, Germany (Reprint); Univ Cologne, Dept Dermatol, D-50931 Cologne, Germany; Univ Cologne, Inst Biochem 2, D-50931 Cologne, Germany; Univ Cologne, Inst Genet, D-50931 Cologne, Germany; Univ Witten Herdecke, Dept Mol Oncol, Wuppertal, Germany. JOURNAL OF BIOLOGICAL CHEMISTRY (29 MAR 2002) Vol. 277, No. 13, pp. 10789-10794. Publisher: AMER SOC BIOCHEMISTRY MOLECULAR BIOLOGY INC. 9650 ROCKVILLE PIKE, BETHESDA, MD 20814-3996 USA. ISSN: 0021-9258. Pub. country: Germany. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The integrin alpha(2)-subunit was ablated in mice by targeted deletion

of the ITGA2 gene. alpha(2)-Deficient animals develop normally, are fertile, and reproduce. Surprisingly, no obvious anatomical or histological differences were observed in mutant mice. Besides its significance in tissue morphogenesis, integrin alpha(2)beta(1), has been reported to play a major role in hemostasis by mediating platelet adhesion and activation on subendothelial collagen. To define its role in hemostasis, alpha(2)-deficient platelets were analyzed for their capacity to adhere to and aggregate in response to fibrillar or soluble collagen type L We show that aggregation of alpha(2)-deficient platelets to fibrillar collagen is delayed but not reduced, whereas aggregation to enzymatically digested soluble collagen is abolished. Furthermore, alpha(2)-deficient platelets normally adhere to fibrillar collagen. However, in the presence of an **antibody** against GPVI (activating **platelet collagen receptor**), adhesion of alpha(2)-deficient but not wild type platelets is abrogated. These results demonstrate that integrin alpha(2)beta(1), significantly contributes to platelet adhesion to (fibrillar) collagen, which is further confirmed by the abolished adhesion of alpha(2)-deficient platelets to soluble collagen. Thus, alpha(2)beta(1), plays a supportive rather than an essential role in platelet-collagen interactions. These results are in agreement with the observation that alpha(2)beta(1)-deficient animals suffer no bleeding anomalies.

L9 ANSWER 4 OF 15 MEDLINE on STN DUPLICATE 3

2002075876 Document Number: 21659770. PubMed ID: 11723134. The platelet receptor GPVI mediates both adhesion and signaling responses to collagen in a receptor density-dependent fashion. Chen Hong; Locke Darren; Liu Ying; Liu Changdong; Kahn Mark L. (Department of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania 19104, USA.) JOURNAL OF BIOLOGICAL CHEMISTRY, (2002 Jan 25) 277 (4) 3011-9. Journal code: 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.

AB The platelet response to collagen is a primary event in hemostasis and thrombosis, but the precise roles of the numerous identified **platelet collagen receptors** remain incompletely defined. Attention has recently focused on **glycoprotein VI** (GPVI), a receptor that is expressed on platelets in association with a signaling adapter, the Fc receptor gamma chain (Fc Rgamma). Genetic and pharmacologic loss of GPVI function results in loss of collagen signaling in platelets, but studies to date have failed to demonstrate that GPVI-Fc Rgamma expression is sufficient to confer collagen signaling responses. These results have led to the hypothesis that collagen responses mediated by GPVI-Fc Rgamma may require the collagen-binding integrin alpha2beta1 as a co-receptor, but this model has not been supported by a recent study of mouse platelets lacking alpha2beta1. In the present study we have used a novel anti-GPVI monoclonal **antibody** to measure the level of GPVI on human platelets and to guide the development of GPVI-expressing cell lines to assess the role of GPVI in mediating platelet collagen responses. GPVI receptor density on human platelets appears tightly regulated, is independent from the level of alpha2beta1 expression, and significantly exceeds that on previously characterized GPVI-expressing RBL-2H3 cells. Using newly generated GPVI-expressing RBL-2H3 cells with receptor densities equivalent to that on human platelets, we demonstrate that GPVI expression confers both adhesive and signaling responses to collagen in a graded fashion that is proportional to the GPVI receptor density. These results resolve some of the conflicting data regarding GPVI-collagen interactions and demonstrate that 1) GPVI-Fc Rgamma expression is sufficient to confer both adhesion and signaling responses to collagen, and 2) GPVI-mediated collagen responses are receptor density-dependent at the receptor levels expressed on human platelets.

L9 ANSWER 5 OF 15 MEDLINE on STN DUPLICATE 4

2001436540 Document Number: 21359356. PubMed ID: 11344165. A novel viper venom metalloproteinase, alborhagin, is an agonist at the **platelet collagen rec ptor** GPVI. Andrews R K; Gardiner E E;

Asazuma N; Berlanga O; Tulasne D; Nieswandt B; Smith A I; Berndt M C; Watson S P. (Hazel and Pip Appel Vascular Biology Laboratory and the Peptide Biology Laboratory, Baker Medical Research Institute, Melbourne 8008, Australia.. rkandrews@hotmail.com) . JOURNAL OF BIOLOGICAL CHEMISTRY, (2001 Jul 27) 276 (30) 28092-7. Journal code: 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.

AB The interaction of platelet membrane **glycoprotein VI** (GPVI) with collagen can initiate (patho)physiological thrombus formation. The viper venom C-type lectin family proteins convulxin and alboaggregin-A activate platelets by interacting with GPVI. In this study, we isolated from white-lipped tree viper (Trimeresurus albolabris) venom, alborhagin, which is functionally related to convulxin because it activates platelets but is structurally different and related to venom metalloproteinases. Alborhagin-induced platelet aggregation (EC50, <7.5 microg/ml) was inhibitable by an anti-alphaIIbbeta3 **antibody**, CRC64, and the Src family kinase inhibitor PP1, suggesting that alborhagin activates platelets, leading to alphaIIbbeta3-dependent aggregation. Additional evidence suggested that, like convulxin, alborhagin activated platelets by a mechanism involving GPVI. First, alborhagin- and convulxin-treated platelets showed a similar tyrosine phosphorylation pattern, including a similar level of phospholipase Cgamma2 phosphorylation. Second, alborhagin induced GPVI-dependent responses in GPVI-transfected K562 and Jurkat cells. Third, alborhagin-dependent aggregation of mouse platelets was inhibited by the anti-GPVI monoclonal **antibody** JAQ1. Alborhagin had minimal effect on convulxin binding to GPVI-expressing cells, indicating that these venom proteins may recognize distinct binding sites. Characterization of alborhagin as a GPVI agonist that is structurally distinct from convulxin demonstrates the versatility of snake venom toxins and provides a novel probe for GPVI-dependent platelet activation.

L9 ANSWER 6 OF 15 MEDLINE on STN DUPLICATE 5

2001398776 Document Number: 21326192. PubMed ID: 11352922. Rhodocytin (aggretin) activates platelets lacking alpha(2)beta(1) integrin, **glycoprotein VI**, and the ligand-binding domain of glycoprotein Ibalpha. Bergmeier W; Bouvard D; Eble J A; Mokhtari-Nejad R; Schulte V; Zirngibl H; Brakebusch C; Fassler R; Nieswandt B. (Department of Molecular Oncology, General Surgery, Witten/Herdecke University, Arrenbergerstr. 20, Haus 10, 42117 Wuppertal, Germany.) JOURNAL OF BIOLOGICAL CHEMISTRY, (2001 Jul 6) 276 (27) 25121-6. Journal code: 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.

AB Although alpha(2)beta(1) integrin (glycoprotein Ia/IIa) has been established as a **platelet collagen receptor**, its role in collagen-induced platelet activation has been controversial. Recently, it has been demonstrated that rhodocytin (also termed aggretin), a snake venom toxin purified from the venom of Calloselasma rhodostoma, induces platelet activation that can be blocked by monoclonal **antibodies** against alpha(2)beta(1) integrin. This finding suggested that clustering of alpha(2)beta(1) integrin by rhodocytin is sufficient to induce platelet activation and led to the hypothesis that collagen may activate platelets by a similar mechanism. In contrast to these findings, we provided evidence that rhodocytin does not bind to alpha(2)beta(1) integrin. Here we show that the Cre/loxP-mediated loss of beta(1) integrin on mouse platelets has no effect on rhodocytin-induced platelet activation, excluding an essential role of alpha(2)beta(1) integrin in this process. Furthermore, proteolytic cleavage of the 45-kDa N-terminal domain of glycoprotein (GP) Ibalpha either on normal or on beta(1)-null platelets had no significant effect on rhodocytin-induced platelet activation. Moreover, mouse platelets lacking both alpha(2)beta(1) integrin and the activating collagen receptor GPVI responded normally to rhodocytin. Finally, even after additional proteolytic removal of the 45-kDa N-terminal domain of GPIbalpha rhodocytin induced aggregation of these platelets. These results demonstrate that rhodocytin induces platelet activation by mechanisms that are fundamentally different from those induced by collagen.

L9 ANSWER 7 OF 15 MEDLINE on STN DUPLICATE 6

2001370835 Document Number: 21226781. PubMed ID: 11278467. Expression and function of the collagen receptor GPVI during megakaryocyte maturation. Lagrue-Lak-Hal A H; Debili N; Kingbury G; Lecut C; Le Couedic J P; Villeval J L; Jandrot-Perrus M; Vainchenker W. (INSERM E9907, Faculte Xavier Bichat, 75870 Paris Cedex 18, Paris, France.) JOURNAL OF BIOLOGICAL CHEMISTRY, (2001 May 4) 276 (18) 15316-25. Journal code: 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.

AB In this report, the expression and function of the **platelet collagen receptor glycoprotein VI** (GPVI) were studied in human megakaryocytes during differentiation and maturation of mobilized blood and cord blood derived CD34(+) cells. By flow cytometry, using an anti-GPVI monoclonal **antibody** or convulxin, a GPVI-specific ligand, GPVI was detected only on CD41(+) cells including some CD41(+)/CD34(+) cells, suggesting expression at a stage of differentiation similar to CD41. These results were confirmed at the mRNA level using reverse transcription-polymerase chain reaction. GPVI expression was low during megakaryocytic differentiation but increased in the more mature megakaryocytes (CD41(high)). As in platelets, megakaryocyte GPVI associates with the Fc receptor gamma chain (FcRgamma). The FcR gamma chain was detected at the RNA and protein level at all stages of megakaryocyte maturation preceding the expression of GPVI. The other collagen receptor, alpha(2)beta(1) integrin (CD49b/CD29), had a pattern of expression similar to GPVI. Megakaryocytic GPVI was recognized as a 55-kDa protein by immunoblotting and ligand blotting, and thus it presented a slightly lower apparent molecular mass than platelet GPVI (58 kDa). Megakaryocytes began to adhere to immobilized convulxin via GPVI after only 8-10 days of culture, at a time when megakaryocytes were maturing. At this stage of maturation, they also adhered to immobilized collagen by alpha(2)beta(1) integrin-dependent and -independent mechanisms. Convulxin induced a very similar pattern of protein tyrosine phosphorylation in megakaryocytes and platelets including Syk, FcRgamma, and PLC(gamma)2. Our results showed that GPVI is expressed early during megakaryocytic differentiation but functionally allows megakaryocyte adherence to collagen only at late stages of differentiation when its expression increases.

L9 ANSWER 8 OF 15 MEDLINE on STN

2001272329 Document Number: 21231159. PubMed ID: 11331578. **Glycoprotein VI** but not alpha2beta1 integrin is essential for platelet interaction with collagen. Nieswandt B; Brakebusch C; Bergmeier W; Schulte V; Bouvard D; Mokhtari-Nejad R; Lindhout T; Heemskerk J W; Zirngibl H; Fassler R. (Department of Molecular Oncology, General Surgery, Witten/Herdecke University, 42117 Wuppertal, Germany.. nieswand@klinikum-wuppertal.de) . EMBO JOURNAL, (2001 May 1) 20 (9) 2120-30. Journal code: 8208664. ISSN: 0261-4189. Pub. country: England: United Kingdom. Language: English.

AB Platelet adhesion on and activation by components of the extracellular matrix are crucial to arrest post-traumatic bleeding, but can also harm tissue by occluding diseased vessels. Integrin alpha2beta1 is thought to be essential for platelet adhesion to subendothelial collagens, facilitating subsequent interactions with the activating **platelet collagen receptor, glycoprotein VI** (GPVI). Here we show that Cre/loxP-mediated loss of beta1 integrin on platelets has no significant effect on the bleeding time in mice. Aggregation of beta1-null platelets to native fibrillar collagen is delayed, but not reduced, whereas aggregation to enzymatically digested soluble collagen is abolished. Furthermore, beta1-null platelets adhere to fibrillar, but not soluble collagen under static as well as low (150 s(-1)) and high (1000 s(-1)) shear flow conditions, probably through binding of alphaIIbbeta3 to von Willebrand factor. On the other hand, we show that platelets lacking GPVI can not activate integrins and consequently fail to adhere to and aggregate on fibrillar as well as soluble collagen. These data show that GPVI plays the central role in

platelet-collagen interactions by activating different adhesive receptors, including alpha2beta1 integrin, which strengthens adhesion without being essential.

L9 ANSWER 9 OF 15 MEDLINE on STN DUPLICATE 7
2001258216 Document Number: 21102921. PubMed ID: 11181698. Long-term antithrombotic protection by in vivo depletion of platelet **glycoprotein VI** in mice. Nieswandt B; Schulte V; Bergmeier W; Mokhtari-Nejad R; Rackebrandt K; Cazenave J P; Ohlmann P; Gachet C; Zirngibl H. (Department of Molecular Oncology, General Surgery, Witten/Herdecke University, 42117 Wuppertal, Germany.. nieswand@klinikum-wuppertal.de) . JOURNAL OF EXPERIMENTAL MEDICINE, (2001 Feb 19) 193 (4) 459-69. Journal code: 2985109R. ISSN: 0022-1007. Pub. country: United States. Language: English.

AB Coronary artery thrombosis is often initiated by abrupt disruption of the atherosclerotic plaque and activation of platelets on the subendothelial layers in the disrupted plaque. The extracellular matrix protein collagen is the most thrombogenic constituent of the subendothelial layer; therefore, a selective inhibition of the collagen activation pathway in platelets may provide strong antithrombotic protection while preserving other platelet functions. Here we demonstrate that treatment of mice with a monoclonal **antibody** against the activating **platelet collagen receptor glycoprotein VI** (GPVI; JAQ1) results in specific depletion of the receptor from circulating platelets and abolished responses of these cells to collagen and collagen-related peptides (CRPs). JAQ1-treated mice were completely protected for at least 2 wk against lethal thromboembolism induced by infusion of a mixture of collagen (0.8 mg/kg) and epinephrine (60 microg/ml). The tail bleeding times in JAQ1-treated mice were only moderately increased compared with control mice probably because the treatment did not affect platelet activation by other agonists such as adenosine diphosphate or phorbol myristate acetate. These results suggest that GPVI might become a target for long-term prophylaxis of ischemic cardiovascular diseases and provide the first evidence that it is possible to specifically deplete an activating glycoprotein receptor from circulating platelets in vivo.

L9 ANSWER 10 OF 15 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
2002:129535 Document No.: PREV200200129535. The **platelet collagen receptor glycoprotein VI** (GPVI) signals through lipid rafts in a Fc Rgamma-dependent manner. Locke, Darren [Reprint author]; Chen, Hong [Reprint author]; Liu, Chang-Dong [Reprint author]; Kahn, Mark L. [Reprint author]. Molecular Cardiology, University of Pennsylvania, Philadelphia, PA, USA. Blood, (November 16, 2001) Vol. 98, No. 11 Part 1, pp. 25a. print.
Meeting Info.: 43rd Annual Meeting of the American Society of Hematology, Part 1. Orlando, Florida, USA. December 07-11, 2001. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971. Language: English.

AB The **platelet collagen receptor** GPVI signals through the immunoreceptor tyrosine activation motif (ITAM) of its co-receptor Fc Rgamma using many of the same downstream signaling proteins as T cell, B cell and Fc receptors. Signaling by these immune receptors is believed to proceed from receptor clustering to ITAM tyrosine phosphorylation by the src family kinases Fyn and Lyn and subsequent activation of the tyrosine kinases Syk or ZAP-70. Activation of immune receptors results in receptor movement to cholesterol-rich areas of the cell membrane known as lipid rafts that are enriched in Fyn, Lyn and the transmembrane adaptor protein LAT and are defined by their resistance to solubilization by non-ionic detergents. To determine whether activation of GPVI results in receptor movement to lipid rafts we expressed GPVI in RBL-2H3 cells, a mast cell line which expresses abundant Fc Rgamma but no known collagen receptors. Activation of GPVI with the agonist convulxin resulted in a rapid, transient movement of GPVI receptors to lipid rafts, a response which was also seen with activation of endogenous Fc epsilon

receptors which also couple to Fc Rgamma. The mechanism by which immune receptor activation results in receptor movement to lipid rafts is unknown. To determine the contribution of Fc Rgamma for GPVI movement to lipid rafts we examined the behavior of GPVI R272L, a previously characterized mutant GPVI receptor in which a single amino acid substitution results in loss of Fc Rgamma coupling and intracellular signaling despite normal surface expression. GPVI R272L binds CVX but does not move to lipid rafts following ligand binding, suggesting that GPVI receptor movement to lipid rafts is mediated by the Fc Rgamma chain. The role of lipid rafts in platelet signaling by GPVI and other receptors has not been defined. Using a novel anti-GPVI monoclonal **antibody**, HY101, we have isolated lipid rafts from human platelets and shown that, like GPVI-expressing RBL-2H3 cells, platelet stimulation of GPVI by convulxin results in the transient movement of GPVI to lipid rafts. Our results demonstrate that (1) during GPVI signaling the receptor moves to lipid rafts in both RBL-2H3 cells and in human platelets, and (2) GPVI movement to lipid rafts following ligand binding is driven by associated Fc Rgamma chain and is not a simple consequence of ligand-induced receptor clustering. Studies are presently underway to determine whether GPVI-Fc Rgamma movement to lipid rafts is required for ITAM phosphorylation or vice-versa and to better define the role of lipid rafts for signaling by collagen in human platelets.

L9 ANSWER 11 OF 15 CAPLUS COPYRIGHT 2003 ACS on STN

2000:569621 Document No. 133:250251 Expression and function of the mouse collagen receptor **glycoprotein VI** is strictly dependent on its association with the FcR.gamma. chain. Nieswandt, Bernhard; Bergmeier, Wolfgang; Schulte, Valerie; Rackebrandt, Kirsten; Gessner, J. Engelbert; Zirngibl, Hubert (Department of Molecular Oncology, General Surgery, University of Witten-Herdecke, Wuppertal, 42283, Germany). Journal of Biological Chemistry, 275(31), 23998-24002 (English) 2000. CODEN: JBCHA3. ISSN: 0021-9258. Publisher: American Society for Biochemistry and Molecular Biology.

AB Platelet glycoprotein (GP) VI has been proposed as the major collagen receptor for activation of human platelets. Human GPVI belongs to the Ig superfamily and is noncovalently assocd. with the FcR.gamma. chain that is involved in signaling through the receptor. In mice, similar mechanisms seem to exist, as platelets from FcR.gamma. chain-deficient mice do not aggregate in response to collagen. However, the activating collagen receptor on mouse platelets has not been definitively identified. In the current study the authors examd. the function and in vivo expression of GPVI in control and FcR.gamma. chain-deficient mice with the first monoclonal **antibody** against GPVI (JAQ1). On wild type platelets, JAQ1 inhibited platelet aggregation induced by collagen but not PMA or thrombin. Crosslinking of bound JAQ1, on the other hand, induced aggregation of wild type but not FcR.gamma. chain-deficient platelets. JAQ1 stained platelets and megakaryocytes from wild type but not FcR.gamma. chain-deficient mice. Furthermore, JAQ1 recognized GPVI (approx. 60 kDa) in immunopptn. and Western blot expts. with wild type but not FcR.gamma. chain-deficient platelets. These results strongly suggest that GPVI is the collagen receptor responsible for platelet activation in mice and demonstrate that the assocn. with the FcR.gamma. chain is crit. for its expression and function.

L9 ANSWER 12 OF 15 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN

2000:305460 The Genuine Article (R) Number: 304DB. A new platelet receptor specific to type III collagen - Type III collagen-binding protein. Monnet E; FauvelLefeve F (Reprint). UNIV PARIS 07, INST HEMATOL, HOP ST LOUIS, INSERM, U353, 1 AVE CLAUDE VELLEFAUX, F-75475 PARIS 10, FRANCE (Reprint); UNIV PARIS 07, INST HEMATOL, HOP ST LOUIS, INSERM, U353, F-75475 PARIS 10, FRANCE. JOURNAL OF BIOLOGICAL CHEMISTRY (14 APR 2000) Vol. 275, No. 15, pp. 10912-10917. Publisher: AMER SOC BIOCHEMISTRY MOLECULAR BIOLOGY INC. 9650 ROCKVILLE PIKE, BETHESDA, MD 20814. ISSN: 0021-9258. Pub. country: FRANCE. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Platelet interaction with type III collagen is mediated by several platelet receptors that recognize specific sequences in collagen. We previously described an octapeptide KP*GEP*GPK within the alpha(1)III-CB4 fragment that binds to platelets and specifically inhibits platelet aggregation induced by type III collagen. In this study, we demonstrated that the octapeptide prevented platelet contact and spreading on type III collagen and subendothelium under static and flow conditions. Platelets adhered to the immobilized octapeptide, and **antibodies** directed against other **platelet collagen receptors** (glycoprotein (GP) Ia/IIa, GP IV, p65, p47) did not impair this adhesion. The platelet octapeptide receptor was identified by ligand blotting as a protein doublet with molecular masses of 68 and 72 kDa and does not correspond to any other already known **platelet collagen receptors** (GP Ia, GP TV GP VI, and p65), Our results indicate that a specific type III collagen receptor, expressed on the platelet surface, is involved in the first stages of platelet type III collagen interaction.

L9 ANSWER 13 OF 15 CAPLUS COPYRIGHT 2003 ACS on STN
2000:344942 Document No. 133:116381 Cloning and Expression of the Platelet-Specific Collagen Receptor **Glycoprotein VI**.
Miura, Y.; Ohnuma, M.; Jung, S. M.; Moroi, M. (Institute of Life Science, Department of Protein Biochemistry, Kurume University, Fukuoka, Japan). Thrombosis Research, 98(4), 301-309 (English) 2000. CODEN: THBRAA. ISSN: 0049-3848. Publisher: Elsevier Science Inc..
AB Platelet **glycoprotein VI** (GP VI) was purified from platelet membranes and its internal amino acid sequences were detd. The cloned cDNA of GP VI indicates an open reading frame coding for 20 amino acid signal sequences and a mature protein of 319 amino acids. Its extracellular region has two Ig-like domains and a mucin-like, Ser/Thr-rich region, suggesting that GP VI is a member of the paired Ig-like receptor family. GP VI-transfected cells contained convulxin-(reactive) and **antibody** against recombinant GP VI-reactive protein bands that migrated at the same position as platelet GP VI in SDS/PAGE-electroblotting. These data indicate that the protein deduced from the cloned cDNA corresponds to platelet GP VI.

L9 ANSWER 14 OF 15 MEDLINE on STN DUPLICATE 8
1999436101 Document Number: 99436101. PubMed ID: 10506151. The **platelet collagen receptor glycoprotein VI** is a member of the immunoglobulin superfamily closely related to FcalphaR and the natural killer receptors.
Clemetson J M; Polgar J; Magnenat E; Wells T N; Clemetson K J. (Theodor Kocher Institute, University of Berne, Freiestrasse 1, CH-3012 Berne, Switzerland.. clemetson@tki.unibe.ch) . JOURNAL OF BIOLOGICAL CHEMISTRY, (1999 Oct 8) 274 (41) 29019-24. Journal code: 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.
AB We have cloned the **platelet collagen receptor** glycoprotein (GP) VI from a human bone marrow cDNA library using rapid amplification of cDNA ends with platelet mRNA to complete the 5' end sequence. GPVI was isolated from platelets using affinity chromatography on the snake C-type lectin, convulxin, as a critical step. Internal peptide sequences were obtained, and degenerate primers were designed to amplify a fragment of the GPVI cDNA, which was then used as a probe to screen the library. Purified GPVI, as well as Fab fragments of polyclonal **antibodies** made against the receptor, inhibited collagen-induced platelet aggregation. The GPVI receptor cDNA has an open reading frame of 1017 base pairs coding for a protein of 339 amino acids including a putative 23-amino acid signal sequence and a 19-amino acid transmembrane domain between residues 247 and 265. GPVI belongs to the immunoglobulin superfamily, and its sequence is closely related to FcalphaR and to the natural killer receptors. Its extracellular chain has two Ig-C2-like domains formed by disulfide bridges. An arginine residue is found in position 3 of the transmembrane portion, which should permit association with Fcgamma and its immunoreceptor tyrosine-based activation motif via a salt bridge. With 51 amino acids, the cytoplasmic tail is relatively long

and shows little homology to the C-terminal part of the other family members. The ability of the cloned GPVI cDNA to code for a functional **platelet collagen receptor** was demonstrated in the megakaryocytic cell line Dami. Dami cells transfected with GPVI cDNA mobilized intracellular Ca(2+) in response to collagen, unlike the nontransfected or mock transfected Dami cells, which do not respond to collagen.

L9 ANSWER 15 OF 15 MEDLINE on STN DUPLICATE 9
90037566 Document Number: 90037566. PubMed ID: 2808700. A patient with platelets deficient in **glycoprotein VI** that lack both collagen-induced aggregation and adhesion. Moroi M; Jung S M; Okuma M; Shinmyozu K. (Department of Biochemistry II, Jichi Medical School, Tochigi, Japan.) JOURNAL OF CLINICAL INVESTIGATION, (1989 Nov) 84 (5) 1440-5. Journal code: 7802877. ISSN: 0021-9738. Pub. country: United States. Language: English.
AB Molecular level studies on platelets deficient in collagen-induced aggregation provide evidence for identifying possible **platelet collagen receptors**. We investigated platelets from a patient with mild bleeding time prolongation, but otherwise normal coagulation data. Her platelets lacked collagen-induced aggregation and adhesion, but retained normal aggregation and release by other agonists. Labeling her platelets with 125I or 3H and analysis by SDS-PAGE/autoradiography showed normal levels of glycoproteins Ia, Ib, IIa, IIb, IIIa, and IV. However, there were significantly decreased incorporations of both radioactivities into a 61-kD membrane glycoprotein (GP), which was identified as GPVI from its mobility on unreduced-reduced, two-dimensional SDS-PAGE. Sugiyama et al. (1987. Blood. 69: 1712) reported that the serum from an idiopathic thrombocytopenic purpura (ITP) patient contained an **antibody** against a 62-kD platelet protein. Our patient's platelets lacked the antigen for the ITP patient's **antibody**, demonstrating that the ITP serum contains a specific **antibody** against GPVI. The patient's parents' platelets contained approximately 50% the normal amount of GPVI, but still had normal collagen-induced aggregation and adhesion. The patient's platelets did not bind to types I and III collagen fibrils. Our results suggest that GPVI functions as a collagen receptor.

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     21 NOV 2003
L1          4638 S SINGLE CHAIN ANTIBODY
L2             0 S L1 AND GLYCOPROTIEN IV
L3           709 S GLYCOPROTEIN IV
L4            13 S GLYCOPROTEIN VI ANTIBOD?
L5             9 DUP REMOVE L4 (4 DUPLICATES REMOVED)
L6           775 S GLYCOPROTEIN VI
L7           163 S L6 AND PLATELET COLLAGEN RECEPTOR
L8            46 S L7 AND ANTIBOD?
L9            15 DUP REMOVE L8 (31 DUPLICATES REMOVED)

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L10            0 L8 AND SINGLE CHAIN

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qian m?/au or kingbury g?/au)
L11         5083 (VILLEVAL J?/AU OR JAMDROT-PERRUS M?/AU OR VAINCHENCKER W?/AU
                 OR GILL D?/AU OR QIAN M?/AU OR KINGBURY G?/AU)

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L12            3 L11 AND TANGO 268
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L13 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2003 ACS on STN
2002:793461 Document No. 137:305773 Antibodies to **TANGO 268** sequence homolog of glycoprotein VI and their possible diagnostic or therapeutic uses. Busfield, Samantha J.; **Villeval, Jean-Luc**; Jandrot-Perrus, Martine; **Vainchencker, William**; **Gill, Davinder Singh**; Qian, Diana Ming; Kingsbury, Gillian (Millennium Pharmaceuticals, Inc., USA). PCT Int. Appl. WO 2002080968 A1 20021017, 237 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-US11122 20020409. PRIORITY: US 2001-829495 20010409.

AB The invention provides isolated nucleic acid mols. and polypeptide mols. that encode glycoprotein VI, a platelet membrane glycoprotein that is involved platelet-collagen interactions. The invention also provides antisense nucleic acid mols., expression vectors contg. the nuclei acid mols. of the invention, host cells into which the expression vectors have been introduced, and non-human transgenic animals in which a nucleic acid mol. of the invention has been introduced or disrupted. The invention still further provides isolated polypeptides, fusion polypeptides, antigenic peptides and antibodies. Diagnostic, screening and therapeutic methods utilizing compns. of the invention are also provided.

L13 ANSWER 2 OF 3 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
2001:339372 Document No.: PREV200100339372. Nucleic acid molecules encoding glycoprotein VI and recombinant uses thereof. Busfield, Samantha J. [Inventor]; **Villeval, Jean-Luc** [Inventor, Reprint author]. Needham, MA, USA. ASSIGNEE: Millennium Pharmaceuticals, Inc.. Patent Info.: US 6245527 June 12, 2001. Official Gazette of the United States Patent and Trademark Office Patents, (June 12, 2001) Vol. 1247, No. 2. e-file.
CODEN: OGUPE7. ISSN: 0098-1133. Language: English.

AB The invention provides isolated **TANGO 268** nucleic acid molecules and polypeptide molecules. **TANGO 268** encodes a polypeptide that represents glycoprotein VI, a platelet membrane glycoprotein that is involved platelet-collagen interactions. The invention also provides antisense nucleic acid molecules, expression vectors containing the nucleic acid molecules of the invention, host cells into which the expression vectors have been introduced, and non-human transgenic animals in which a nucleic acid molecule of the invention has been introduced or disrupted. The invention still further provides isolated polypeptides, fusion polypeptides, antigenic peptides and antibodies. Diagnostic, screening and therapeutic methods utilizing compositions of the invention are also provided.

L13 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2003 ACS on STN
2001:12605 Document No. 134:81775 Glycoprotein VI cDNA and protein from human and murine blood platelets and their diagnostic and therapeutic applications. Busfield, Samantha J.; Villelal, Jean-luc; Jandrot-Perrus, Martine; **Vainchencker, William**; **Gill, Davinder Singh**; **Qian, Ming Diana**; Kingsbury, Gillian (Millennium Pharmaceuticals, Inc., USA). PCT Int. Appl. WO 2001000810 A1 20010104, 227 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN,

CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US18152 20000630. PRIORITY: US 1999-345468 19990630; US 1999-454824 19991206; US 2000-503387 20000214.

AB The invention provides isolated cDNA mols. and polypeptide mols. that encode human and murine glycoprotein VI, a platelet membrane glycoprotein that is involved platelet-collagen interactions. The protein initially designated **TANGO 268** represents the platelet-expressed collagen receptor glycoprotein VI (GPVI) based on the following evidence: (1) the glycosylated mol. wts. of **TANGO 268** and GPVI are identical or similar; (2) both are recognized by anti-GPVI antibodies and bind to convulxin; (3) both are preferentially expressed in megakaryocytic cells; (4) both ar predicted to have a single N-glycosylation site; (5) the mol. mass of GPVI upon N- and O-linked glycosylation is .apprx.62 kDa, that of GPVI; (6) two Ig-like domains in **TANGO 268** indicates interaction with FcR.gamma.; (7) the absence of a large intracytoplasmic tail suggests that this membrane-bound glycoprotein has no signaling role but assocs. with another member of the Ig family; and (8) **TANGO 268** has a charged arginine residue in the transmembrane domain which is also predicted to be present in GPVI. The human gene for GPVI was mapped on radiation hybrid panels to the long arm of chromosome 19, in the region 19q13, syntenic to mouse chromosome 7. The invention also provides antisense nucleic acid mols., expression vectors contg. the nucleic acid mols. of the invention, host cells into which the expression vectors have been introduced, and non-human transgenic animals in which a nucleic acid mol. of the invention has been introduced or disrupted. The invention still further provides isolated polypeptides, fusion polypeptides, antigenic peptides and antibodies. Diagnostic, screening and therapeutic methods utilizing compns. of the invention are also provided.

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COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	97.19	97.40

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-3.91	-3.91

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